Module 4: CLL/SLL

Danielle M. Brander, MD

Director, CLL & Lymphoma Clinical Research

Division Hematologic Malignancies & Cellular Therapy

Duke Cancer Institute

18 February 2023

Discussion Question

How do you choose between venetoclax/obinutuzumab and a Bruton tyrosine kinase (BTK) inhibitor for your patients with previously untreated chronic lymphocytic leukemia (CLL)? When you opt for a BTK inhibitor, which one do you generally prefer and why? Are there any situations in which you feel it is appropriate to combine a BTK inhibitor with venetoclax outside of a clinical trial?

HOW DO YOU CHOOSE BETWEEN VENETOCLAX/OBINUTUZUMAB AND A BTK INHIBITOR FOR YOUR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)?

- Currently, no results from clinical trials comparing the two regimens head to head but ongoing trials will start to answer (some) of these comparisons
- The key considerations in discussing the two treatment regimens
  - Patient specific factors (co-morbidities, concurrent medications)
  - Disease specific factors including cytogenetic/molecular features (TP53 aberrations) and disease presentation (bulky disease, cytopenias, etc)
  - Regimen specific factors (continuous vs fixed duration, oral vs combination, patient preference)
- Difficult, important unknowns: cost, best sequence of agents, how to monitor response
- Important to continue frontline clinical trials for patients with CLL

WHEN YOU OPT FOR A BTK INHIBITOR, WHICH ONE DO YOU GENERALLY PREFER AND WHY?

- BTK inhibitors
  - Covalent: first and second generation, approved/available
    - Ibrutinib
    - Acalabrutinib
    - Zanubrutinib
  - Noncovalent: only in clinical trials for CLL
    - Pirtobrutinib (LOXO-305) – recently available for MCL
    - Others: nemtabrutinib (MK-1026/ARQ-531), vecabrutinib (SNS-062), LP-168b
- Toxicities of special interest with BTK inhibitor treatment
  - Differences or similarities between agents
  - Discontinuation rates
- Head to head trials – efficacy and safety
  - ELEVATE-R/R
  - ALPINE
- Trials for patients intolerant to BTK inhibitors

COMBINING A BTK INHIBITOR WITH VENETOCLAX – WHAT ARE THE IMPORTANT CONSIDERATIONS?

- Clinical trials
  - MDACC PH2 study – ibrutinib and venetoclax
  - CAPTIVATE clinical trial – MRD driven and fixed duration cohorts
- Ongoing clinical trials and important questions for BTK and BCL2 combinations:
  - Use of second generation and alternative BTKi
  - Duration of therapy/combination
  - Retreatment
- Outside of clinical trials – consider clinical trials

Discussion Question

How do you envision pirtobrutinib and chimeric antigen receptor (CAR) T-cell therapy eventually fitting into the treatment algorithm for CLL?

HOW DO YOU ENVISION PIRTOBRUTINIB AND CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY EVENTUALLY FITTING INTO THE TREATMENT ALGORITHM FOR CLL?

- Pirtobrutinib: available for MCL, not CLL outside of clinical trials
- Efficacy and safety of pirtobrutinib
  - Double refractory/double exposed CLL
  - AE/AE of special interest for BTK inhibitor
- Comment on monotherapy and combination therapy trials of pirtobrutinib

HOW DO YOU ENVISION PIRTOBRUTINIB AND CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY EVENTUALLY FITTING INTO THE TREATMENT ALGORITHM FOR CLL?

- CAR-T in CLL
  - Efficacy and safety
  - Timing and disease bulk likely important
  - Other considerations: BTK inhibitors and CAR-T, other cellular therapies for CLL

- Summary: Identifying areas of unmet need in CLL
  - Double exposure/refractory
  - Intolerance
  - Richter's transformation

Discussion Question

How do you approach therapy for patients with relapsed follicular lymphoma, and where do lenalidomide, copanlisib, tazemetostat, CAR T-cell therapy and mosunetuzumab fit in?

HOW DO YOU APPROACH THE TREATMENT OF PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA (FL)?

- Identifying when patients with relapsed follicular lymphoma need treatment
- Identifying high risk patients on relapse: POD24
- Identifying patients with transformed disease: when biopsy is indicated
- Treatment options for relapsed follicular lymphoma requiring therapy (no particular order)
  - Chemoimmunotherapy
  - Lenalidomide + anti-CD20ab
  - PI3K inhibitors (copanlisib)
  - EZH2 inhibitor (tazemetostat)
  - CAR-T
  - Clinical trials

Discussion Question

When administering a BTK inhibitor to a patient with relapsed/refractory (R/R) mantle cell lymphoma (MCL), which one do you generally prefer and why? Are there are situations in which you feel it is appropriate to administer a BTK inhibitor in the first-line setting outside of a clinical trial?

Discussion Question

How do you approach the treatment of multiregimen-relapsed MCL, and where do venetoclax, pirtobrutinib and CAR T-cell therapy fit in?

HOW DO YOU APPROACH PATIENTS WITH RELAPSED MANTLE CELL LYMPHOMA?

- Clinical trials
- BTK inhibitors
  - Covalent/Irreversible: ibrutinib (+/- antiCD20), acalabrutinib, zanubrutinib
  - Noncovalent/reversible: pirtobrutinib
  - Other considerations for BTK inhibitors in MCL: frontline use, combination therapy (with CIT or venetoclax), patient selection/cautions
- Other options in relapsed disease
  - Chemoimmunotherapy (+/- BTK)
  - Lenalidomide regimens
  - CAR-T (after BTKi) – brexucabtagene autoleucel

Thank you

Danielle M Brander, MD

Duke Cancer Institute

Danielle.brander@duke.edu